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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/29/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/816,081	ROZEMA ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 10/5/2006, in which claims 1-18 were canceled, and claims 24-32 were newly added. Currently, claims 19-32 are pending.

Election/Restrictions

Applicant's election without traverse of Group II in the reply filed on 9/18/2006 is acknowledged. All pending claims are readable upon elected Group II.

An examination on the merits of claims 19-32 follows.

Response to Amendment

The amendment to the claims filed on 10/5/2006 does not comply with the requirements of 37 CFR 1.121(c) because any claim added by amendment must be indicated with the status of "new" and presented in clean version, *i.e.*, **without any underlining**. Amendments to the claims filed on or after July 30, 2003 must comply with 37 CFR 1.121(c) which states:

(c) *Claims*. Amendments to a claim must be made by rewriting the entire claim with all changes (*e.g.*, additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

(1) *Claim listing.* All of the claims presented in a claim listing shall be presented in ascending numerical order. Consecutive claims having the same status of "canceled" or "not entered" may be aggregated into one statement (*e.g.*, Claims 1–5 (canceled)). The claim listing shall commence on a separate sheet of the amendment document and the sheet(s) that contain the text of any part of the claims shall not contain any other part of the amendment.

(2) *When claim text with markings is required.* All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended," and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended," or "withdrawn" if also being amended, shall include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn—currently amended."

(3) *When claim text in clean version is required.* The text of all pending claims not being currently amended shall be presented in the claim listing in clean version, *i.e.*, without any markings in the presentation of text. The presentation of a clean version of any claim having the status of "original," "withdrawn" or "previously presented" will constitute an assertion that it has not been changed relative to the immediate prior version, except to omit markings that may have been present in the immediate prior version of the claims of the status of "withdrawn" or "previously presented." Any claim added by amendment must be indicated with the status of "new" and presented in clean version, *i.e.*, without any underlining.

(4) *When claim text shall not be presented; canceling a claim.*

(i) No claim text shall be presented for any claim in the claim listing with the status of "canceled" or "not entered."

(ii) Cancellation of a claim shall be effected by an instruction to cancel a particular claim number. Identifying the status of a claim in the claim listing as "canceled" will constitute an instruction to cancel the claim.

(5) *Reinstatement of previously canceled claim.* A claim which was previously canceled may be reinstated only by adding the claim as a "new" claim with a new claim number.

The nature of the noncompliance did not preclude the examination on the merits of claims 19-32, the results of which are presented below. In response to this Office action, Applicant must provide a claim listing in compliance with 37 CFR 1.121(c).

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 2/8/2005, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19 and 20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 8, 9 and 10 of U.S. Patent No. 7,138,382 (hereinafter the '382 patent).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 19 and 20 are generic to all that is recited in claims 1, 8 and 9 of the

'382 patent. That is, claims 1, 8 and 9 of the '382 patent fall entirely with the scope of claims 19 and 20 of the instant application or, in other words, instant claims 19 and 20 are anticipated by claims 1, 8 and 9 of the '382 patent. Specifically, the conflicting claims are drawn to a process of transfecting a nucleic acid into a cell in vivo, comprising attaching a membrane activity inhibitor to a membrane active peptide via a labile linkage, wherein the inhibitor is detached within the cell, adding the peptide to a solution containing the nucleic acid, delivering the peptide and nucleic acid to the cells, wherein the peptide and nucleic acid are endocytosed, and transfecting the cell. The conflicting claims are narrower in scope than the instant claims in that they specify the structure of the membrane active polymer as a peptide (claim 1), a melittin peptide (claim 8). Claim 1, 8 and 9 are narrower in scope than instant claim 19, because they are limited to the delivery of a nucleic acid molecule, whereas instant claim 9 reads on the delivery of any molecule.

Thus, the instant claims, if allowed, would extend patent protection of the invention of the '382 patent. Further, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the rights to the '382 invention, then two different assignees would hold patent claims to the claimed invention.

Claims 19 and 20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 9 of U.S. Patent No. 6,630,351 (hereinafter the '351 patent).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the

reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 19 and 20 are generic to all that is recited in claims 1, 2 and 9 of the '351 patent. That is, claims 1, 2 and 9 of the '351 patent fall entirely with the scope of claims 19 and 20 of the instant application or, in other words, instant claims 19 and 20 are anticipated by claims 1, 2 and 9 of the '351 patent. Specifically, the conflicting claims are drawn to a process for transfecting a nucleic acid into a cell in vitro, comprising attaching a reversible labile membrane activity inhibitor to a membrane active polymer (claim 9), peptide (claim 2) or melittin peptide (claim 1), adding the polymer or peptide to a solution containing the nucleic acid, contacting the peptide and nucleic acid with the cell, wherein the polymer or peptide and nucleic acid is endocytosed, and transfecting the cell. The conflicting claims are narrower in scope than the instant claims in that they specify the structure of the membrane active polymer as a peptide (claim 2), a melittin peptide (claim 1). Claim 1, 2 and 9 are narrower in scope than instant claim 19, because they are limited to the delivery of a nucleic acid molecule, whereas instant claim 9 reads on the delivery of any molecule.

Thus, the instant claims, if allowed, would extend patent protection of the invention of the '351 patent. Further, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the rights to the '351 invention, then two different assignees would hold patent claims to the claimed invention.

Claims 19 and 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19, 21, 23, 25 and 26 of copending Application No. 10/083,456 (hereinafter the '456 application).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 19 and 20 are generic to all that is recited in claims 19, 21, 23, 25 and 26 of the '456 application. That is, claims 19, 21, 23, 25 and 26 of the '456 application fall entirely with the scope of claims 19 and 20 of the instant application or, in other words, instant claims 19 and 20 are anticipated by claims 19, 21, 23, 25 and 26 of the '456 application. Specifically, conflicting 19 and the claims that depend therefrom are narrower in scope than the instant claims in that the membrane active compound is a non-viral complex, and the molecule that is delivered is limited to a nucleic acid.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 recites the limitation "the cell" in line 1. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to recite the limitation "a cell."

Claims 20-32 depend from claim 19 and thus are indefinite for the same reasons applied to claim 19.

The term "maleic anhydride derivatives" in claim 26 is a relative term that renders the claim indefinite. The term "maleic anhydride derivatives" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. One of ordinary skill in the art would not know how much one could vary the structure of maleic anhydride and meet the limitations of the claimed invention.

Claim 29 is vague and indefinite in that the metes and bounds of the phrase "at least about" are unclear. It is unclear if the phrase is referring to a molecular weight of at least 10,000 Daltons or a molecular weight of about 10,000 Daltons. It would be remedial to amend the claim language to clearly indicate the molecular weights encompassed by the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 19, 20 and 24-28 are rejected under 35 U.S.C. 102(a) as being anticipated by Rozema et al (Bioconjugate Chem. Vol. 14, pages 51-57, published online 12/19/2002, cited on the IDS filed 2/8/2005; see the entire reference).

Regarding claim 19, Rozema et al teach a method for delivering a phosphorodiamidate morpholino oligonucleotide (PMO) molecule to the cytoplasm of a cell, comprising the steps of (i) associating the PMO with CDM-melittin to form a complex by providing relatively high concentrations of the compounds in the tissue culture dish containing the cells, and (ii) delivering the complex to HeLa cells by co-endocytosis of the oligonucleotide and melittin (e.g. page 53, Oligonucleotide Delivery Assay; pages 55-56, Delivery of Oligonucleotide; page 56, right column, 2nd full paragraph). CDM-melittin is a maleic anhydride derivative of the membrane active peptide melittin, which reversibly modifies the ε amino groups of the melittin peptide (e.g. page 51, right column).

Regarding claim 20, the phosphorodiamidate morpholino oligonucleotide (PMO) used in the method of Rozema et al is a polynucleotide: CCTCTTACCTCAGTTACAATTTATA (e.g. page 53, Oligonucleotide Delivery Assay).

Regarding claim 24, the melittin peptide used in the method of Rozema et al is a polyamine, because the peptide contains multiple arginine and lysine residues: GIGAILKVLATGLPTLISWIKNKRKQ (e.g. page 54, right column, 1st full paragraph).

Regarding claim 25, the reversible inhibitors are CDM, 2-propionic-3-methylmaleic anydride or carboxylated dimethyl maleic acid (e.g. page 51, right column). A maleamate is a maleic anhydride that reacts with amines to form pH-labile amides, which is what is formed by the reaction of CDM with melittin (e.g. page 51, right column).

Regarding claim 26, CDM is a disubstituted maleamate (e.g. Figure 1).

Regarding claim 27, the CDM-melittin used by Rozema et al is a disubstituted maleic anhydride derivative obtained from the reaction of the membrane active melittin peptide with disubstituted carboxydimethylmaleic anhydride (e.g. Figure 1; page 52, Acylation of Melittin with CDM, Dimethylmaleic, Citraconic, and cis-Aconitic Anhydrides).

Regarding claim 28, the CDM inhibitors are cleaved from the melittin peptide in the endosome (e.g. page 55, Release of Fluorscein-Labeled Polyethylene Glycol from the Endocytic Compartment by CDM-Melittin).

Claims 19, 20, 24 and 29 are rejected under 35 U.S.C. 102(a) as being anticipated by Murthy et al (Bioconjugate Chem. Vol. 14, pages 412-419, published online 1/15/2003, cited on the IDS filed 2/8/2005; see the entire reference).

Regarding claim 19, Murthy et al teach a method for delivering antisense oligonucleotides (AS-ODNs) to the cytoplasm of a cell, comprising the steps of (i) forming a complex of encrypted polymer E2 and the ODN, and (ii) delivering the complex to RAW cells, which endocytose the complex (e.g. page 417, AS-ODN delivery). Encrypted polymer E2 is a reversibly inhibited membrane active polymer (e.g. Figures 1 and 2a). Further, Murthy et al teach a method for delivering a peptide to a cell, comprising the steps of (i) forming a covalent association between FITC-$(His)_6$-$(Gly)_4$-Cys peptide to polymer E3 along with methoxy-PEG-SH, and (ii) delivering the complex to RAW cells, which endocytose the complex (e.g. page 418, right column, 1st full paragraph; Figure 7). Polymer E3 conjugated to methoxy-PEG-SH is a reversibly inhibited membrane active polymer (e.g. Figures 1 and 2b).

Regarding claim 20, Murthy et al teach a method for delivering antisense oligonucleotides (AS-ODNs) to the cytoplasm of a cell, comprising the steps of (i) forming a complex of polymer E2 and the ODN, and (ii) delivering the complex to RAW cells, which endocytose the complex (e.g. page 417, AS-ODN delivery). Polymer E2 is a reversibly inhibited membrane active polymer (e.g. Figures 1 and 2a). The ODN is a polynucleotide.

Regarding claim 24, the encrypted polymer E2 of Murthy et al is a membrane active polyamine with reversible inhibitors linked via pH labile bonds (e.g. Figures 1 and 2a).

Regarding claim 29, the membrane active polymers E2 and E3 of Murthy et al each have a molecular weight of at least 10,000 Daltons (e.g. page 414, paragraph bridging columns; Figure 2).

Claims 19, 20, 24 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoffman et al (WO 01/51092 A2, cited on the IDS filed 2/8/2005; see the entire reference).

Regarding claim 19, Hoffman et al teach a method for delivering a molecule to the cytoplasm of a cell, comprising the steps of (i) making a membrane disruptive agent which may be a hydrophobic polymer which is coupled to a hydrophilic polymer or multiple hydrophilic groups which are released after endocytosis to expose the hydrophobic polymer or hydrophilic polymer which is protonated after endocytosis to yield a hydrophobic polymer, all of which are membrane disruptive and reversibly inhibited, (ii) linking an agent such as DNA plasmids, antisense oligodeoxynucleotides (ODNs) or protein therapeutic to the membrane disruptive agent, and (iii) delivering the complex of agent and membrane disruptive agent to a cell (e.g. page 5, line 18 to page 8, line 3; Examples 5-6).

Regarding claim 20, Hoffman et al teach the method wherein rhodamine-labeled nucleic acid molecules, ODNs, are complexed with polymer E3 and delivered to cells (e.g. Example 6; Figure 4).

Regarding claim 24, Hoffman et al teach a method for delivering a molecule to the cytoplasm of a cell, comprising the steps of (i) making a membrane disruptive agent which may be a hydrophobic polymer which is coupled to a hydrophilic polymer or multiple hydrophilic groups which are released after endocytosis to expose the hydrophobic polymer or hydrophilic polymer which is protonated after endocytosis to yield a hydrophobic polymer, all of which are membrane disruptive and reversibly inhibited (ii) linking an agent such as DNA plasmids, antisense oligodeoxynucleotides (ODNs) or protein therapeutic to the membrane disruptive agent, and (iii) delivering the complex of agent and membrane disruptive agent to a cell (e.g.

page 5, line 18 to page 8, line 3; Examples 5-6). Further, Hoffman et al teach the linking of inhibitor groups to polyamines such as poly [vinyl amine] via a pH labile bond (e.g. page 11, line 30 to page 12, line 28).

Regarding claim 29, Hoffman et al teach the method where the membrane active polymer has a molecular weight of at least 10,000 Daltons (e.g. page 11).

Claims 19, 20 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Sullivan et al (US Patent Application Publication No. 2001/0044147 A1; see the entire reference).

Regarding claim 19, Sullivan et al teach the delivery of nucleic acid molecules to the cytoplasm of a cell, comprising delivering stable polynucleotide delivery vehicles (SPDVs) (e.g. Abstract; paragraphs [0063]-[0064]. Sullivan et al teach the formation of condensed cationic lipid/polynucleotide complex, where cationic and lipid moieties are covalently linked by a labile (e.g., biodegradable of pH labile) linker group, which allow for the production of polynucleotide delivery vehicles comprising cationic lipids which dissociate the lipid and cation moieties after cellular internalization and/or endosomal fusion (e.g. paragraphs [0044]-[0048] and [0054]). Sullivan et al teach embodiments where the lipid is a membrane active polymer (e.g. paragraph [0055]).

Regarding claim 20, Sullivan et al teach the delivery of a polynucleotide of interest with the SPDVs (e.g. paragraphs [0060]-[0064]).

Regarding claim 24, Sullivan et al teach SPDVs comprising a reversibly inhibited membrane active polymer that consists of a plurality of membrane activity inhibitors such as 2-

methyl-maleic anhydride reversibly linked to a membrane active polyamine via pH labile bonds (e.g. paragraphs [0054]-[0056]).

Claims 19-24 and 29-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Schacht et al (US Patent No. 6,312,727 B1; see the entire reference).

Regarding claim 19, Schacht et al teach a method for delivering a nucleic acid molecule to the cytoplasm of a cell, comprising associating the nucleic acid molecule with a membrane active polymer reversibly inhibited with a cleavable group further linked to a hydrophilic polymer and delivering the complex to a cell that internalizes the complex by endocytosis (e.g. column 3, line 44 to column 4, line 15; paragraph bridging columns 7-8; Figure 1).

Regarding claim 20, Schacht et al teach the delivery of polynucleotide molecules with the abovementioned method (e.g. column 5, lines 40-43).

Regarding claims 21-23, Schacht et al teach condensing a polynucleotide with a polycation to form a binary complex, adding a linker to link the polycation of the binary complex and a hydrophilic shell such that the outer shell is subject to cleavage upon a drop in pH within the endosomal or lysosomal compartment, which facilitates the exposure and activation of membrane-active fusogenic or membrane disrupting agents for enabling the DNA to gain access to the cytoplasm of the cell (e.g. column 7, line 28 to column 8, line 11). Further, Schacht et al teach that the hydrophilic polymer may be PEG, a membrane active polymer, or may be modified to be a membrane active polymer itself (e.g. column 8, lines 53-60; column 13, line 42 to column 14, line 2). Moreover, Schacht et al teach that the size of the particles used in the

method are generally less than 70 nm in diameter, and possible approaching an ideal size of 30-40 nm in diameter (e.g. column 8, lines 12-18).

Regarding claim 24, Schacht et al teach the reversible inhibition of polyamine polycations by adding a linker that is linked by a pH-labile bond (e.g. column 7, line 9 to column 8, line 11).

Regarding claim 29, Schacht et al teach the use of membrane active polymers with a molecular weight of at least 10,000 Daltons (e.g. column 12, lines 58-64; Example 11).

Regarding claims 30-32, Schacht et al teach the formation of a salt stable nanoparticle that has a net negative charge for delivery to the cells (e.g. column 8, lines 12-18; column 13, lines 13-16; paragraph bridging columns 13-14).

Claims 19, 20 and 24-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolff (WO 00/75164 A1; see the entire reference).

Regarding claim 19, Wolff et al teach a method for the delivery and release of a compound to a cell, comprising the steps of (i) forming a complex containing the biomolecule and a pH-labile polymer linked to a membrane active compound, and delivering the complex to the cell such that it is endocytosed (e.g. Abstract; page 19, lines 20-25; page 21, line 15 to page 22, line 30; page 23, lines 21-25).

Regarding claim 20, Wolff et al teach the method to delivery polynucleotides (e.g. page 22, line 19; page 23, lines 21-25).

Regarding claim 24, Wolff et al teach the method where the membrane active polymer is a polyamine and is linked to the membrane inhibitor via a pH labile bond (e.g. page 36, line 18 to page 37, line 14; page 47, lines 18-27).

Regarding claims 25-26, Wolff et al teach the use of 2,3-disubstituted maleamic acids as an inhibitor with a pH labile bond (e.g. page 26, lines 1-14; page 59, lines 1-13).

Regarding claims 27 and 28, Wolff et al teach the synthesis of 2-propionic-3-methylmaleic anhydride (carboxydimethylmaleic anhydride or C-DM) and the reaction of this compound to polyamines for use in the abovementioned method (e.g. page 63, lines 1-18; page 65, lines 8-14; page 66, lines 21-27; Example 7).

Regarding claim 29, Wolff et al teach the use of polymers that are at least 10,000 Daltons (e.g. Example 1).

Claims 19, 20, 24-26 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Wolff et al (US Patent No. 7,138,382 B2; see the entire reference).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding claims 19 and 20, Wolff et al teach a method for delivering a nucleic acid molecule to a cell *in vivo*, comprising the steps of (i) associating the nucleic acid molecule with a

reversibly inhibited membrane active polymer such as a peptide or melittin peptide to form a complex, and (ii) delivering the complex to the cells, wherein the complex is endocytosed by the cell (e.g. column 12, line 31 to column 14, line 37; paragraph bridging columns 16-17; claims 1, 8 and 9).

Regarding claim 24, Wolff et al teach the use of a pH labile bond to reversibly link a membrane active polyamine to a membrane activity inhibitor (e.g. paragraph bridging columns 16-17).

Regarding claims 25 and 26, Wolff et al teach the use of disubstituted maleamates (amides of 2,3-disubstituted maleamic acid) (e.g. column 18, lines 42-60).

Regarding claim 29, Wolff et al teach the formation of membrane active polymers containing two to about 80 polymers, which would result in a molecular weight of at least about 10,000 Daltons (e.g. column 29, line 53 to column 32, line 8).

Claim19, 20, 24-26 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Monahan et al (US Patent No. 6,630,351 B1; see the entire reference).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding claims 19 and 20, Monahan et al teach a method for delivering a nucleic acid molecule to a cell *in vivo*, comprising the steps of (i) associating the nucleic acid molecule with a reversibly inhibited membrane active polymer such as a peptide or melittin peptide to form a complex, and (ii) delivering the complex to the cells, wherein the complex is endocytosed by the cell (e.g. column 12, line 23 to column 14, line 27; paragraph bridging columns 16-17; claims 1, 2 and 9).

Regarding claim 24, Monahan et al teach the use of a pH labile bond to reversibly link a membrane active polyamine to a membrane activity inhibitor (e.g. paragraph bridging columns 16-17).

Regarding claims 25 and 26, Monahan et al teach the use of disubstituted maleamates (amides of 2,3-disubstituted maleamic acid) (e.g. column 18, lines 29-47).

Regarding claim 29, Monahan et al teach the formation of membrane active polymers containing two to about 80 polymers, which would result in a molecular weight of at least about 10,000 Daltons (e.g. column 29, line 32 to column 31, line 49).

Claims 19, 20, 24-26 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Monahan et al (US Patent Application Publication No. 2003/0199090 A1; see the entire reference).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the

inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding claim 19, Monahan et al teach the delivery of desired compounds into cells by forming a complex with the biomolecule and a pH-labile polymer linked to a membrane active compound, and delivering the complex to the cell such that it is endocytosed (e.g. paragraphs [0063]-[0069]).

Regarding claim 20, Monahan et al teach the delivery of polynucleotide molecules (e.g. paragraph [0063]).

Regarding claim 24, Monahan et al teach the linkage of a membrane activity inhibitor to a membrane active polyamine via a pH labile bond (e.g. paragraphs [0164]-[0174], [0240]).

Regarding claims 25 and 26, Monahan et al teach the use of disubstituted maleic anhydride derivatives as the inhibitor (e.g. paragraph [0257]).

Regarding claim 29, Monahan et al teach the formation of membrane active polymers of at least 10,000 Daltons (e.g. paragraph [0309]).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

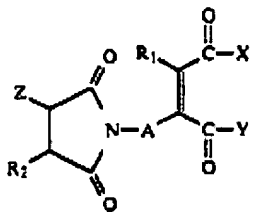
claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schacht et al (US Patent No. 6,312,727 B1; see the entire reference) in view of Blattler et al (US Patent No. 4,569,789; see the entire reference).

The teachings of Schachet et al are described above and applied as before.

Schachet et al do not teach maleamates linked to a membrane active polyamine via pH labile bonds.

Blattler et al teach monosubstituted maleamate derivative crosslinking agent of the following structure:



where one of X and Y is O^- and the other of X and Y is the residue of the amino-group containing substance whose amino nitrogen forms an amide link (e.g. Claim 1). Blattler et al teach that the crosslinking agents permit controlled release of an amino-group-containing substance under mildly acidic conditions (e.g. column 2, lines 45-68). Further, Blattler et al teach that the amino-linkage can be formed under mild conditions that does not affect the

structure of the molecule to which is linked (e.g. protein) but can yield a strong bond that is not cleaved prematurely (e.g. column 6, lines 19-63).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide delivery method of Schacht et al to include the maleamate crosslinker taught by Blattler et al because Schachet et al teach it is within the ordinary skill in the art to use a pH-labile linker in the polynucleotide delivery complex and Blattler et al teach that the maleamate linker is pH labile and can be used for cell-delivery of compounds (e.g. column 5, lines 24-68).

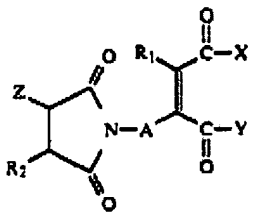
One would have been motivated to make such a modification in order to receive the expected benefit of using a crosslinker that can be used under mild conditions that do not affect the structure of the molecule to which it is linked and can still yield a strong bond that is cleaved under mildly acidic conditions as taught by Blattler et al, which would result in the release of the polynucleotide of Schachet et al within the endosome or lysosome. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sullivan et al (US Patent Application Publication No. 2001/0044147 A1; see the entire reference) in view of Blattler et al (US Patent No. 4,569,789; see the entire reference).

The teachings of Sullivan et al are described above and applied as before.

Sullivan et al do not teach maleamates linked to a membrane active polyamine via pH labile bonds.

Blattler et al teach monosubstituted maleamate derivative crosslinking agent of the following structure:



where one of X and Y is O^- and the other of X and Y is the residue of the amino-group containing substance whose amino nitrogen forms an amide link (e.g. Claim 1). Blattler et al teach that the crosslinking agents permit controlled release of an amino-group-containing substance under mildly acidic conditions (e.g. column 2, lines 45-68). Further, Blattler et al teach that the amino-linkage can be formed under mild conditions that does not affect the structure of the molecule to which is linked (e.g. protein) but can yield a strong bond that is not cleaved prematurely (e.g. column 6, lines 19-63).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide delivery method of Sullivan et al to include the maleamate crosslinker taught by Blattler et al because Sullivan et al teach it is within the ordinary skill in the art to use a pH-labile linker in the polynucleotide delivery complex and Blattler et al teach that the maleamate linker is pH labile and can be used for cell-delivery of compounds (e.g. column 5, lines 24-68).

One would have been motivated to make such a modification in order to receive the expected benefit of using a crosslinker that can be used under mild conditions that do not affect the structure of the molecule to which it is linked and can still yield a strong bond that is cleaved under mildly acidic conditions as taught by Blattler et al, which would result in the release of the polynucleotide of Sullivan et al within the endosome or lysosome. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
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jad

CELINE QIAN, PH.D.
PRIMARY EXAMINER